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HETEROSEXUAL AIDS

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March 1996



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HETEROSEXUAL AIDS

When AIDS first arose in the United States in the early 1980s, it was dubbed "gay-related immunodeficiency disease" (GRID) because it appeared to afflict only homosexual and bisexual men. As more cases were diagnosed, however, it became apparent that one did not have to be gay or even male in order to acquire HIV. So dramatically has the face of AIDS changed that P.J. Hitchcock, Chief of the Sexually Transmitted Diseases Branch at the United States National Institute of Allergy and Infectious Diseases, estimates that today, world-wide, more women than men are infected with HIV. This estimate is based upon a number of scientific studies which showed that in heterosexual transmission of HIV women are at least twice as susceptible as men.⁽¹⁾

The World Health Organization estimates that heterosexual transmission has accounted for 75% of the HIV infections in adults world-wide.⁽²⁾ The remaining 25% are primarily due to the use of contaminated blood and blood products, needle sharing by intravenous drug users, and homosexual/bisexual transmission. Heterosexual intercourse has been the dominant route of transmission in Africa, Asia, South America, Central America and the Caribbean. Indeed, in the United States, AIDS ceased being primarily a disease of gay men in the early 1990s. Data from the United States Centers for Disease Control and Prevention show that the proportion of new cases reported among homosexual/bisexual men decreased from 47.3% in 1993 to 43.3% in 1994. While the rate of AIDS among American gay males decreases, there has been a recorded increase among women and minority groups. Women accounted for 18.1% of total AIDS cases in 1994, up from 16.2% in 1993. In the

(1) J. Cohen, "Women: Absent Term in the AIDS Research Equation," *Science*, Vol. 269, August 1995, p. 777-780.

(2) World Health Organization, *The HIV/AIDS pandemic: 1993 Overview*, Geneva, World Health Organization, 1993, Publication No. WHO/GPA/CNP/EVA/93.1.

same years, the number of American Blacks with AIDS increased from 36.1% to 39% of total new cases, while Hispanics with AIDS increased from 17.7% to 18.7%.⁽³⁾

Only in Canada and the developed nations of Europe and Australasia does AIDS remain a disease where the majority of those afflicted are gay. Even in these countries, however, HIV is making its way into the heterosexual population. In England and Wales, AIDS projections for 1995 to 1999 indicate that the number of new cases among homosexuals and bisexuals will drop by 7% but there will be a rise of 29% among intravenous drug users and a 25% increase due to heterosexual transmission of the virus.⁽⁴⁾ The Canadian Public Health Association estimates that currently one in 10,000 Canadians is living with AIDS, and one in 1,000 is currently infected with HIV. The number of cases of AIDS in Canada attributed to heterosexual activity continues to rise at a faster rate than for any other risk category. In 1991, the number of women diagnosed with AIDS in Canada was one third of the number of reported cases among women in the previous ten years combined. Many women have been identified as HIV-positive when visiting doctors during the course of pregnancy. In British Columbia and the Yukon, one pregnant woman in 3,745 is infected; in Toronto, it is one in 1,976; and, in Montreal one in 616.⁽⁵⁾ A Quebec HIV seroprevalence study conducted between July 1989 and June 1993 revealed that one in 555 women undergoing abortion in Montreal was HIV-positive.⁽⁶⁾

As of 31 December 1995, women comprised 6.2% of all diagnosed cases of AIDS in Canada. The coast-to-coast distribution of female AIDS cases, however, is quite uneven. Women comprise 2.8% of the AIDS cases in British Columbia, 4.8% in Alberta, 4.5% in Ontario; but 10.1% in Quebec and in the Atlantic provinces.⁽⁷⁾ Further, Health Canada data, compiled to 31 December 1994, show that women comprised 19.5% (9 of 46) of

(3) M.H. Cooper, "Combating AIDS," *CQ Researcher*, Vol. 5, 1995, p. 345-368.

(4) S. Ramsay, "English HIV and AIDS Projections Made," *The Lancet*, Vol. 347, 1996, p. 109.

(5) Canadian Foundation for AIDS Research, "HIV/AIDS Statistics," January 1996, 2 p.

(6) R.S. Remis, *et al.*, "HIV Infection among Women Undergoing Abortion in Montreal," *Canadian Medical Association Journal*, Vol. 153, 1995, p. 1271-1279.

(7) Health Canada, *Quarterly Surveillance Update: AIDS in Canada*, January 1996, p. 4.

the AIDS cases diagnosed in Newfoundland.⁽⁸⁾ It is recognized that immigration to Quebec from countries with a high incidence of HIV infection, and intravenous drug use in Montreal have contributed to the higher incidence of HIV infection among women in Quebec; however, reasons for the situation in Atlantic Canada are not immediately apparent. Clarification of this question may reveal some of the factors that place heterosexual Canadians at risk for HIV/AIDS.

MALE TO FEMALE TRANSMISSION OF HIV

Unprotected heterosexual intercourse with an HIV-positive male may result in the vaginal deposition of HIV-contaminated semen. In this situation, the HIV is received in a moist, warm, relatively non-oxidative environment that may protect and prolong the life of the virus until it is able to infect susceptible host tissue. In contrast, intercourse with an HIV-positive female may expose the external male genitalia to HIV-contaminated vaginal secretions; however, subsequent exposure to cold, oxygen and the drying effects of air are likely to inactivate the virus. In addition, skin acts as an effective barrier, leaving only a portion of the penis unprotected against possible infection. Thus, unprotected sexual intercourse with an HIV-infected partner puts females at greater risk than males.

The HIV virus readily infects CD4 T-lymphocytes⁽⁹⁾ because the HIV viral envelope has a protein structure that dovetails with the CD4 structure (receptor site) on the lymphocyte cell wall. The cells on the surface of the female genital tract (the epithelial cells) lack CD4 receptor sites; however, T-lymphocytes are attracted to the vaginal and cervical epithelia if inflammation or lesions are present. Accordingly, it is believed that women are more apt to acquire an HIV infection if there are perturbations to the epithelium lining of the genital tract. This theory has been verified by studies that show women with sexually

(8) Health Canada, *Quarterly Surveillance Update: AIDS in Canada*, January 1995, p. 10.

(9) Lymphocytes are a variety of white blood cell which are involved in immunity. There are B-lymphocytes and T-lymphocytes. The B-lymphocytes produce circulating antibodies. T-lymphocytes, which are produced in the thymus gland, directly kill invading bacteria and viruses by engulfing them.

transmitted diseases (STDs), which cause lesions and inflammation, have a much higher risk of HIV infection.⁽¹⁰⁾

In addition to T-lymphocytes, macrophages and Langerhans cells, both key immune system cells, bear CD4 receptor sites. In animal studies, these cells have been observed to be present in the tissue immediately under the epithelial cells. Further, the epithelial layer has been observed to swell and thin during different phases of the menstrual cycle. Theoretically, a microscopic lesion in the epithelial layer could provide HIV with the opportunity of coming in contact with the CD4-bearing cells below. It has also been observed that women with cervical ectopy, a condition that disrupts the epithelial lining, are particularly vulnerable to HIV infection. It is currently believed that both the cervix and vagina can provide sites for the entry of HIV.⁽¹¹⁾

The foregoing describes infection by free viral particles. There also appears to be some evidence that infection can be accomplished by intracellular-HIV present in lymphocytes carried with semen. Electron micrograph studies have shown that the infected lymphocytes attach to the epithelial cells of the female genital tract. Intracellular HIV particles settle to the bottom of the cells and are then released to the spaces between the lymphocytes and the epithelial cells. The epithelial cells, without the benefit of CD4-receptor sites, then engulf viral particles and become infected. Although these studies were conducted with human cell lines derived from the cervix, animal studies indicate that intracellular virus may be far less infectious than free virus. Specifically, macaques monkeys were easily infected with simian immunodeficiency virus (SIV), the simian cousin of HIV, when small doses of free SIV were placed in their vaginas. In contrast, no infections occurred when large doses of lymphocyte-associated SIV were applied in an identical fashion to a second test group of macaques.⁽¹²⁾

(10) Cohen (August 1995).

(11) *Ibid.*

(12) *Ibid.*

FEMALE TO MALE TRANSMISSION OF HIV

Separate studies designed to estimate the per-contact probability of female to male transmission of HIV have shown that Thai and Kenyan males who engage in sex with local prostitutes are, at a minimum, 31 times more likely to acquire HIV than are North American males who engage in sex with local prostitutes.^{(13),(14),(15)} This very large difference in infection probability has allowed researchers to probe into the reasons why the incidence of heterosexual AIDS is much higher in developing countries and to determine the factors that place men at risk.

Sexual exposure, including the number of partners, the frequency of intercourse, and the frequency of prostitute contact in some populations may differ between countries. The observed differences in HIV-1 seroprevalence, however, would require profound differences in sexual activity, for which there are few supportive data. This realization has led researchers to look for factors that either increase infectivity or render exposed individuals more susceptible to HIV.

In the Kenyan study, the sexual health of 293 men who frequented Nairobi prostitutes (85% HIV-positive) was followed. Newly acquired HIV infection was associated with frequent prostitute contact, with the acquisition of genital ulcer disease, and with being uncircumcised. After a single sexual exposure, 43% of all uncircumcised men who acquired an ulcer became HIV-positive. In contrast, all of the circumcised study subjects who did not acquire an ulcer remained free of HIV infection. Data analysis indicated that lack of circumcision was a greater risk factor than acquisition of a genital ulcer.

In the Thai study of 1,115, 21-year-old male military conscripts, sex with female prostitutes was identified as the principal source of HIV infection. Surveys of the local

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- (13) T.D. Mastro, *et al.*, "Probability of Female-to-Male Transmission of HIV-1 in Thailand," *The Lancet*, Vol. 343, 1994, p. 204-207.
 - (14) D.W. Cameron, *et al.*, "Female to Male Transmission of Human Immunodeficiency Virus Type 1: Risk Factors for Seroconversion in Men," *The Lancet*, Vol. 2 (issue 8660), 1989, p. 403-407.
 - (15) M. Fischl, *et al.*, "Evaluation of Heterosexual Partners, Children, and Household Contact of Adults with AIDS," *Journal of the American Medical Association*, Vol. 257, 1987, p. 640-644.

prostitute population revealed very high rates of STDs, with seropositivity rates of: HIV, 51%; syphilis, 37%; genital herpes, 80%; and chancroid ulcerative disease, 21%. Active infection rates were: chlamydia infection, 30%; gonorrhoea infection 24%; and genital ulcer disease, 9%. For sexually active military conscripts, the highest rate of HIV seroconversion occurred among men who reported both a high frequency of contact with prostitutes and a high rate of STDs. Transmission probability was, however, still quite high for men who frequented prostitutes but did not report STDs. The effect of circumcision on the risk of infection could not be determined as circumcision is very uncommon in Buddhist Thailand.

Male genital ulceration present at the time of exposure to an HIV-positive woman could act as a portal of entry. Genital ulcers, however, are very painful and it is thought that very few men afflicted in this way would engage in sexual intercourse. Rather, it is thought that genital ulcer disease raises the infectivity of an HIV-infected woman by increasing virus shedding in the female genital tract. Researchers have been able to isolate HIV from the surface of genital ulcers, and it is postulated that this condition attracts HIV-infected lymphocytes and macrophages to the ulcer and results in high concentrations of infectious virus in vaginal secretions. It is believed that other STDs may also potentiate female to male HIV transmission in a similar fashion.

In addition to the Kenyan investigation, other studies have indicated that lack of circumcision places males at greater risk for HIV.^{(16),(17)} Evidence indicates that the male portal of entry for HIV is the glans urethra and the epidermis of the glans penis and/or subprepuce. It has been suggested that the prepuce (foreskin) may physically trap infected vaginal secretions and provide a hospitable environment that enhances viral survival. Minor inflammatory conditions are more common in uncircumcised males, and the foreskin may be more susceptible to traumatic epithelial disruption during sexual intercourse; both conditions could attract susceptible lymphocytes and macrophages and place them in contact with HIV.

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- (16) S.K. Hira, *et al.*, "Genital Ulcers and Male Circumcision as Risk Factors for Acquiring HIV-1 in Zambia," *Journal of Infectious Diseases*, Vol. 161, 1990, p. 584-585.
- (17) J.N. Simonsen, *et al.*, "Human Immunodeficiency Virus Infection in Men with Sexually Transmitted Diseases," *New England Journal of Medicine*, Vol. 319, 1988, p. 274-278.

HETEROSEXUAL TRANSMISSION AND THE GENETIC DIVERSITY OF HIV

HIV is characterized by large genetic flexibility, which has given rise to drug resistance and escape from immune responses, and has confounded attempts to develop an effective vaccine.⁽¹⁸⁾ To date, nine genetically distinct subtypes of HIV have been identified and designated subtypes A through H, and O.⁽¹⁹⁾ In Japan and the developed countries of North America, Europe, and Australasia, virtually all HIV infections among homosexuals/bisexuals and intravenous drug users are due to HIV-B. In contrast, B is the least prevalent subtype in Africa, where subtypes A, C, D, and E predominate and are spread by heterosexual transmission. A situation of considerable scientific interest has been identified in south-east Asia, where intravenous drug users are infected with subtype B, while the afflicted heterosexual population is infected with E.

The segregation of subtype B and E between two distinct population groups prompted Thai researchers to quantify the male to female risk of transmission for each of these subtypes. This two-year study monitored the HIV status of women whose male partners were infected with either HIV-E or HIV-B. During the course of this study, 70% of the women with HIV-E infected partners became infected themselves, while only 26% of the women with HIV-B infected partners did so. The researchers suggested that HIV-E presents a higher risk of heterosexual transmission than HIV-B, and they postulated that the very high rate of spread of HIV/AIDS in Thailand might be due to the high heterosexually infectious nature of HIV-E.⁽²⁰⁾

A study conducted at the Harvard School of Public Health in Boston has given additional weight to the theory that subtypes B and E differ in infectivity. Langerhans cells were isolated from the vagina, cervix, breast and penile foreskin and successfully grown in

(18) S. Bonhoeffer, *et al.*, "Causes of HIV Diversity," *Nature*, Vol. 376, 1995, p. 125.

(19) A.W. Artenstein, *et al.*, "Multiple Introductions of HIV-1 Subtype E into the Western Hemisphere," *The Lancet*, Vol. 346, 1995, p. 1197-1199.

(20) C. Kuanusont, *et al.*, "HIV-1 Subtypes and Male-to-Female Transmission in Thailand," *The Lancet*, Vol. 345, 1995, p. 1078-1083.

pure cell cultures. These cell lines were then challenged with either HIV-B or E. It was observed that HIV-B demonstrated very poor growth while HIV-E grew "quite well," particularly on the Langerhans cell lines derived from the female genital tract.⁽²¹⁾ Work at the Pasteur Institute and the University of Alabama have shown that it is much easier to infect a chimpanzee vaginally with subtype E than with subtype B. An animal study at the University of California has shown that when monkeys are vaginally inoculated with SIV, the virus localizes in Langerhans cells.⁽²²⁾

At the September 1995, Third International Conference on AIDS in Asia and the Pacific, it was suggested that there are two distinct HIV-1 epidemics. In developed countries, subtype B is spread primarily through blood and homosexual sex. The second epidemic is occurring primarily in developing countries, and it is driven by non-B subtypes through vaginal sex. It was feared that developed countries will experience a more severe heterosexual epidemic if other HIV subtypes spread into these populations. On this point, it should be noted that subtype E has been identified in Uruguayan military personnel recently returned from a peace-keeping mission in Cambodia,⁽²³⁾ while subtypes A, D and E have been isolated from American servicemen returning from Thailand, Kenya and Uganda.⁽²⁴⁾ American servicemen are routinely tested for HIV; however, HIV testing is voluntary for civilians returning from holiday or business abroad. Therefore, even though non-B subtypes are being detected among military personnel, epidemiologists believe that civilian travel represents the greater risk for the introduction of highly infectious strains of HIV into the heterosexual populations of developed countries.

In South America, Central America, and the Caribbean, HIV/AIDS is primarily a disease of heterosexuals, with subtype B the causative agent. This observation is at odds

(21) J. Cohen, "Differences in HIV Strains May Underlie Disease Patterns," *Science*, Vol. 270, October 1995, p. 30-31.

(22) *Ibid.*

(23) A.W. Artenstein, *et al.*, (1995).

(24) S.K. Brodine, *et al.*, "Detection of Diverse HIV-1 Genetic subtypes in the USA," *The Lancet*, Vol. 346, 1995, p. 1198-1199.

with the theory that B is less transmissible by heterosexual sex than the other HIV subtypes. As yet there are no strong scientific data to explain this discrepancy; however, epidemiologists have suggested that heterosexual anal intercourse might be more common in those parts of the world,⁽²⁵⁾ circumcision less common, and STDs, particularly the ulcerative type, less well controlled.

PREVENTING THE SPREAD OF HIV/AIDS

In Canada, the most common STDs are chlamydia infection, genital herpes, and venereal warts, with gonorrhoea following in a distant fourth place. The Canadian effort to check the spread of STDs has been particularly successful with syphilis; chancroid ulcerative disease is now virtually never seen in Canadians, except for individuals returning from African or Asian trips. Since the acquisition of a venereal infection is a significant HIV risk factor, a strong program to combat STDs is an essential component of the war against AIDS. Also of particular importance is the proper use of condoms. Condoms have been proven effective in reducing the transmission risk of both STDs and HIV,^{(26),(27)} and in Canada they are both available and affordable. In Africa and south-east Asia, frequent prostitute contact has been identified as an HIV risk factor. Any form of casual or anonymous sex places an individual at risk of sexually transmitted diseases; however, sex with Canadian prostitutes should carry considerably less risk than sex with prostitutes in developing countries because of the lower rates of HIV and STDs in Canada, because condoms are recognized and used as an essential tool of the trade, and because of sexual health education programs that have been focused on target groups. Male circumcision is one factor in HIV risk reduction where Canada may start to fall behind, however. The medical benefits of this procedure have been a matter of debate

(25) Cohen (October 1995).

(26) P. Van de Perre, *et al.*, "The Latex Condom, An Efficient Barrier Against Sexual Transmission of AIDS-Related Viruses," *AIDS*, Vol. 1, 1987, p. 49-52.

(27) K.M. Stone, *et al.*, "Primary Prevention of Sexually Transmitted Diseases," *Journal of the American Medical Association*, Vol. 255, 1986, p. 1763-1766.

for decades, and recently some Canadian provinces have removed circumcision from the list of procedures paid for by provincial health care plans. This decision may have to be reconsidered in light of recent findings that lack of circumcision poses an increased risk for the acquisition of HIV.

All HIV subtypes are characterized by a high mutation rate that has endowed this virus with the ability to develop drug resistance quickly. Similarly, the ability to mutate and the existence of nine distinct subtypes have severely frustrated attempts to develop an effective vaccine. Although strong research efforts are continuing in these areas, another proposed line of attack is chemically and/or biologically to challenge the virus at the point of heterosexual transmission, where the virus is particularly vulnerable. Condoms can perform this role; however, many women cannot negotiate safe-sex practices with their partner. It is argued that if the heterosexual path of HIV transmission is to be cut, women must have access to and control over the use of topical microbiocides effective against both HIV and STDs.

The commercially available spermicide nonoxynol-9 (N-9), has received a great deal of attention as a potential vaginal microbiocide for blocking the male to female transmission of HIV. N-9 is a detergent that cripples microbes by disrupting their outer membranes. A capsule has been developed that can release N-9 to the vagina within three minutes of insertion, and continues delivering the compound for up to six hours. Clinical trials of this microbiocide are to be underway in early 1996. Another detergent microbiocide, C316, has been found to be effective against a broader spectrum of pathogens than N-9; it is currently undergoing vaginal suppository safety testing. A San Diego pharmaceutical company has tested the compound n-Docosanol in monkeys. This chemical permits HIV to attach to vaginal epithelial cells but inhibits the passage of genetic material out of the virus. The United States Food and Drug Administration has found that some sulphated polysaccharides are effective in binding to HIV and thereby preventing binding to vaginal epithelial cells. The final avenue of research involves buffering vaginal pH at mildly acidic levels. Work at Harvard University has shown that HIV is inactivated by the naturally acidic environment of the vagina. Since semen is alkaline, within eight seconds of ejaculation vaginal pH is raised to neutrality, providing HIV with a "window of opportunity." A variety

of buffering agents are being screened and tested to find one or more that will inactivate HIV without disturbing the natural microflora of the vagina, or irritating mucosal surfaces.²⁸

In the United States, the National Institute of Allergy and Infectious Diseases is attempting biologically to cut HIV transmission by the development of vaccines to induce mucosal immunity. In animal studies, rhesus monkeys who had received an intramuscular inoculation of killed SIV virus vaccine followed by a series of oral booster doses were found to be immune to a vaginal challenge from SIV. Clinical trials are now being carried out in which human volunteers are receiving an intramuscular inoculation followed by oral doses of a vaccine containing synthetic copies of HIV envelope proteins. These trials are on-going and data are not yet available.

Until a cure for HIV/AIDS is in use, the best defence against the disease continues to be knowledge. The federal and provincial governments are all active in the promotion of education and prevention initiatives that run the breadth of behavioural change (promotion of abstinence, monogamy, reduction in the number of sexual partners) to safe-sex instruction, to the avoidance of shared needles (for drugs and steroids). Knowledge of how the virus is transmitted allows individuals to make personal choices and, most important, makes everyone responsible for his or her own sexual health.

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